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09/463,881	04/18/2000	WILLIAM IAN DAVID	9267.8	6916

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DRINKER BIDDLE & REATH  
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EXAMINER	/
MARSCHEL, ARDIN H	
ART UNIT	PAPER NUMBER
1631	

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17

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

Application No. <b>09/463,881</b>	Applicant(s) <b>David et al.</b>	
Examiner <b>Ardin Marschel</b>	Art Unit <b>1631</b>	

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

1)  Responsive to communication(s) filed on Oct 1, 2002

2a)  This action is FINAL.      2b)  This action is non-final.

3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

### Disposition of Claims

4)  Claim(s) 1-11 is/are pending in the application.

~~REPLIES RECEIVED~~, Claim(s) 12-20 have been canceled.

~~Claims withdrawn from consideration~~

5)  Claim(s) \_\_\_\_\_ is/are allowed.

6)  Claim(s) 1-11 is/are rejected.

7)  Claim(s) 1 is/are objected to.

8)  Claims \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

9)  The specification is objected to by the Examiner.

10)  The drawing(s) filed on \_\_\_\_\_ is/are  accepted or  objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)  The proposed drawing correction filed on \_\_\_\_\_ is:  approved  disapproved by the Examiner. If approved, corrected drawings are required in reply to this Office action.

12)  The oath or declaration is objected to by the Examiner.

### Priority under 35 U.S.C. §§ 119 and 120

13)  Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)  All b)  Some\* c)  None of:

1.  Certified copies of the priority documents have been received.
2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\*See the attached detailed Office action for a list of the certified copies not received.

14)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a)  The translation of the foreign language provisional application has been received.

15)  Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

### Attachment(s)

1)  Notice of References Cited (PTO-892)

4)  Interview Summary (PTO-413) Paper No(s) 15 & 16

2)  Notice of Draftsperson's Patent Drawing Review (PTO-948)

5)  Notice of Informal Patent Application (PTO-152)

3)  Information Disclosure Statement(s) (PTO-1449) ~~see back of sheet~~

6)  Other:

Due to the newly applied rejections, summarized below, the finality of the Office action, mailed 7/1/02, is hereby withdrawn.

The amendment, filed 10/1/02, has been approved for entry and has been entered.

The above amendment included a newly submitted abstract which also has been entered as acceptable.

Applicants' arguments, filed 10/1/02, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

In the REMARKS, filed 10/1/02, applicants requested review of a supervisory patent examiner of the assignment of the instant application to AU 1631 versus transfer to a different technology center under MPEP § 903.08(d). Consideration of said MPEP section has failed to reveal a provision for a request by applicants for such a review. If applicants wish to pursue this issue further, it is suggested that applicants call the Supervisory Patent Examiner listed at the end of this action.

FACTOR SUMMARY FOR LACK OF ENABLEMENT TYPE REJECTIONS:

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex

parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in In re Wands, 8 USPQ2d 1400 at 1404 (CAFC 1988). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, the results of experiments in genetic engineering are unpredictable. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

LACK OF ENABLEMENT REJECTIONS:

Claims 1-11 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The rejection is maintained and reiterated from the previous office action, mailed 7/1/02, directed to a lack of enablement regarding the predictability of convergence of the methodology of the instant claims as each trial structure is found. The

arguments of applicants are responded to below along with the below summarized rejections based on various elements of lack of enablement as they are argued by applicants together also.

The rejection is also maintained and reiterated from the previous office action, mailed 7/1/02, directed to a lack of enablement regarding the determination of a predetermined fitness threshold. The arguments of applicants are responded to below along with the below summarized rejections based on various elements of lack of enablement as they are argued by applicants together also.

SCOPE OF ENABLEMENT REJECTION:

Claims 1-4 and 6-11 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while being enabling for the fitness formula calculation in claim 5 (subject to certain lack of enablement issues regarding the claim 5 formula itself), does not reasonably provide enablement for a generic fitness calculation as in claims 1-4 and 6-11. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make/use the invention commensurate in scope with these claims.

This rejection is also maintained and reiterated from the previous office action, mailed 7/1/02, directed to a lack of scope of enablement regarding the fitness calculation formulation. The arguments of applicants are responded to below

along with the below summarized rejections based on various elements of lack of enablement as they are argued by applicants together also.

RESPONSE TO ARGUMENTS REGARDING VARIOUS LACK OF ENABLEMENT  
REJECTIONS:

The lack of enablement under 35 U.S.C. § 112, first paragraph, regarding a lack of enablement for derivation of fitness and convergence of trial structures during reiterated attempts is maintained and reiterated from the previous office action, mailed 7/1/02. Applicants firstly argue that the examiner's theory is nowhere explicitly stated. In response, a full reconsideration of the office action, mailed 7/1/02, has failed to reveal any examiner "theory" being set forth. Rather, a rejection has been set forth and maintained from a previous office action, which states that undue experimentation is needed for the practice of certain steps in the claims regarding fitness evaluation and convergence of trial structure attempts. It is not understood how this clear statement is a theory. Thus, this argument is non-persuasive as being inconsistent with the factual basis in said previous office actions.

Applicants then argue that the word usage set forth in the phrase "genetic algorithm" indicates a mathematical technique which should not be read literally, but then also acknowledge that said algorithm may be applied to a molecules including those

of biological origin. It is also noted that this argument of applicants has not set forth any reasoning as to why such mathematical techniques would be easier, or more predictable, or simpler than purely molecular biology techniques. It is also noted that said mathematical techniques, as genetic algorithms, are instantly applied to molecular modeling wherein molecular structures are modeled via analyzing parameters such as variables of molecular structure, fitness of trial structures, etc. which are also of the same type and character as utilized for biological molecular structures. Thus, the complexities and unpredictability of practice of a genetic algorithm is reasonably interpreted as equivalent to a purely biological system analysis, albeit acknowledging that biological system analysis is an option also within the practice of the instant invention.

Applicants then acknowledge as true that a probability of success of practicing the instant invention cannot be determined. In response, such un-determinable probability of success is the essence of unpredictability and is thus a reasonable basis for this rejection as also apparently agreed with by applicants. Applicants then also admit that the practice of a predetermined threshold is not used to guard against divergent processes which additionally supports the lack of predictability of success of the instant invention. Applicants then argue that said threshold is utilized to stop the process when it succeeds. This argument

again supports the basis for this rejection, which is based on a lack of predictability of success for the practice of the instant invention, because this argument of applicants lacks any support for predictability of success, but apparent unpredictable trials and errors. Applicants then further argue that the predetermined threshold is "implicitly" a number less than the fitness value of the initial population. Such an "implicit" predetermination of said threshold has not been argued by applicants as being disclosed as filed. Such arguments, which lack support in the instant application as filed, fail to cure what is apparently a missing significant guidance regarding threshold predetermination as filed. It is noted that the enablement of an invention is based on the explicit disclosure as filed and not upon later filed guidance in arguments during the prosecution history of an application, especially admitted by applicants as being implicit rather than explicit.

Applicants then argue that the instant invention has no relationship to genetic engineering. This conflicts with applicants' admission that biological molecules, reasonably interpreted as those utilized during genetic engineering, are also options for analysis in the instant invention. Additionally, applicants are herein reminded of a discussion above in this action which illustrates the equivalent complexities between genetic engineering and genetic algorithms

as instantly claimed.

Applicants then argue that the Examiner is expected to be familiar with the general knowledge of the person skilled in the art in response to a request for documentation regarding fitness calculation. In response the Examiner was attempting to assist the applicants in overcoming the rejection by a suggestion for supplying relevant documents that may be helpful in this regard. General knowledge of a person skilled in the art does not require specific knowledge of every detail in the art. A fitness calculation is reasonably a detailed knowledge area which may be generally known but not necessarily specifically well known for a specific invention area. It is also pointed out that applicants have acknowledged significant specificity of invention practice by the combined discussion regarding differences between genetic engineering and genetic algorithms as well as requesting review of subject matter assignment within the Patent Office Technology Centers. Applicants then submit documents which are characterized as teaching samples and research papers without dates of publication, including from the internet, as well as citations from Worthington et al. In response enablement is determined as of the filing date of the instant application. The dates of publication, therefore, of documents to illustrate knowledge in the art, of those skilled therein, are critical to support such enablement evaluation. Thus, these un-dated; or

some with post-filing dates; documents cannot be reasonably utilized for a determination of what was known by those of skill in the relevant art at the time of the instant application.

Applicants then argue that the "simultaneous" fitting issue stated in the previous office action on page 6, line 24, through page 7, line 4, is not understood and additionally argue that a better indication of fitness is likely to be afforded by both X-ray and neutron diffraction data than any one set of data alone. In response, the instant claims require the comparison of a calculated fitness with a threshold. This apparently is at least performed by comparing two numbers, one being a fitness. The issue set forth in said page 6-7 is regarding a lack of enabling disclosure by which to combine two diffraction data sets of values into one fitness which then is compared to said threshold. Without some combining methodology, conflicting results are likely to frequently occur wherein evaluation confusion will result as to which fitness comparison to said threshold controls the outputting of a successful trial structure as in the last two lines of instant claim 1.

Applicants then argue that the purpose of the Examiner's remark is not understood regarding trial structure diffraction data determination. In response it is acknowledged that calculated diffraction data for trial structures may be reasonably calculated.

Applicants then argue that packing is easily calculated for a real crystal or a trial structure and is a proper datum for assessing similarity of a real crystal and trial structure. In response the packing of a crystal or structure is acknowledged as reasonably a characteristic of either a real crystal or trial structure, but that nowhere in applicants' arguments is there guidance or instructions as to what is performed for structure comparison, much less, a particular value of fitness which then may be compared to a threshold. Thus, the allegation of applicants regarding packing as being a useful fitness evaluation characteristic is lacking in evaluation guidance which would support enablement of such usage and thus is a non-persuasive argument.

Applicants then argue that the notation in the chi-squared equation is supported by an internet tutorial. This argument is non-persuasive as this tutorial is not documented as being available at the time of filing. It is reiterated from above that the evaluation of enablement is performed as of the instant application filing date. Applicants further argue that switching from one function of two arguments to a function of reduced, or one argument, is so well understood in the art as not to require explanation. In response, such reduction of arguments in a function is well known to be practiced by setting the "removed" argument(s) to a constant thus leaving any remaining argument(s)

as variables. Without setting forth the constant value to be set for the reduced variable(s), this practice is arbitrary and unpredictable as to the result and thus fails to be persuasive regarding overcoming this rejection regarding parameters in the claim 5 chi-squared equation. It is noted that such a tutorial has no requirement to meet enablement standard(s) under 35 U.S.C. § 112, first paragraph.

Applicants next argument regarding scale factor acknowledges that a scale factor gets rid of apparently irrelevant extrinsic variables without supporting what is irrelevant therein. The arguments regarding the scale factor usage is lacking in definition as to what is performed in order to use this factor. Without specific guidance someone wishing to utilize such a factor is left to total and thus undue experimentation as to its value.

Applicants then discuss the eight factors from *In re Wands* and criticizes the rejection as lacking in a *prima facie* case being presented. In response each factor is briefly discussed as follows:

(A) The breadth of claims is broad and generic regarding mathematical methodology and thus covers a vast number of options for fitness, for example, and other parameter determinations thus setting forth a significant burden for the enablement of such breadth.

(B) The nature of the invention is complex as discussed above regarding the claimed genetic algorithm elements.

(c) The state of the prior art is acknowledged by applicants as being relatively undeveloped regarding complex structure determinations and also agreed with by the examiner. Further the below set forth prior art rejection reveals a specific prior art disclosure which falls within the instant claims, but like the state of the art, is specific as to calculation details, rather than generic in calculation practice as applicants allege, albeit without supplying supportive documentation with publication dates on or before the instant filing date.

(D) The level of ordinary skill in the art is significantly high in order to properly manipulate complex mathematical algorithms.

(E) The level of predictability in the art is low as it is well acknowledged that the 3-dimensional structural details of complex structures such as proteins etc. still are generally a mystery as to how to predict such structures from basic information such as the sequence thereof or a list of atoms therein.

(F) The amount of direction provided by the inventor is insufficient as summarized in the above lack of enablement rejections.

(G) Working examples are not provided. Results are shown in various Figures but without sufficient example as to what specific calculational details were utilized regarding them.

(H) The quantity of experimentation needed to perform the instant invention is high due to the complex mathematical details of the evaluation of fitness and a threshold therefor, especially considering the wide range of molecular structures to apply the instant invention to wherein atom to atom etc. interactions and bonding are not only numerous but also well known to be each and every one made up of a complex set of force fields which theoretically extend to infinity in all directions.

PRIOR ART REJECTION:

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1 and 6-11 are rejected under 35 U.S.C. § 102(a) as being clearly anticipated by Kariuki et al. [Chemical Physics Letters 280:189-195(1997)].

Kariuki et al. discloses the various steps of instant claim 1 as follows. The providing step of powder diffraction pattern

is disclosed on page 191, second column, last 7 lines. The generating of lines 4-8 of instant claim 1 is disclosed on pages 192, first column, lines 1-7, via unit cell and space group descriptions which reduce the data from the three dimensional diffraction pattern information to density, unit cell, etc. data values as also present in instant claim 8. The determining and assigning of trial structure data variables as related to the powder data coordinates as in lines 9-12 of instant claim 1 are disclosed on page 192, first column, lines 8-30, relative to the space group as also noted as being carried through the computation as described in Table 1 on page 194 table legend. The calculating of lines 13-14 of a fitness in the reference is detailed on page 191, first column. The determining of whether a fitness is less than or equal to a threshold and the selection of a survivor trial structure for further calculation is disclosed in Kariuki et al. on pages 190-191, especially on page 191, bridging paragraph between the first and second columns, wherein progeny trial structures are selected via the fitness being proportionally better for selected progeny. Additionally, on page 191, first column, lines 2-9, the low value of fitness parameter, R, represents high or better fitness for selection of retained progeny. Since the instant claims are directed to selection based on a less than threshold fitness as apparently a parameter value, this corresponds to the low R value being a

numeric fitness value wherein the threshold is predetermined to be evaluated by comparison to other progeny with a higher and therefore less good fitness. When the predetermined threshold is met of 100 or 200 trial structures of best fitness, that is, lowest R value, as depicted in Figures 2 or 3 on page 193 of the reference the final structure was selected for outputting as also required in the last 3 lines of instant claim 1 and instant claim 10. Additionally, included is the additional outputting of a structure after Rietveld refinement as disclosed on page 193-194 wherein simulated annealing considering bond angles, hydrogen bonding etc. is specifically described on page 193, second column, lines 2-27, as also required in instant claim 11. It is noted that this threshold fitness is a combination of best progeny and a numeric value for the number of evolutionary steps. The instant claims, however, do not limit the complexity of the threshold which is utilized for the various steps regarding fitness evaluation or the final outputting step. Instant claims 6, 7, and 9 are included as rejected hereinunder due to the coordinate and angle disclosures in the reference on page 192, first full paragraph.

A copy of a previously executed IDS, which has been reconsidered, is enclosed to ensure that applicants have been sent a copy of the executed PTO 1449.

The disclosure is objected to because of the following

informalities:

In claim 1, penultimate line, the word "on" in the phrase "at least on trial molecular crystal structure" appears to be a misspelling in context.

Correction is required.

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703)308-4242 or (703)305-3014.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ardin Marschel, Ph.D., whose telephone number is (703)308-3894. The examiner can normally be reached on Monday-Friday from 8 A.M. to 4 P.M.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, Ph.D., can be reached on (703)308-4028.

Any inquiry of a general nature or relating to the status of this application should be directed to Legal Instrument Examiner, Tina Plunkett, whose telephone number is (703)305-3524 or to the Technical Center receptionist whose telephone number is (703) 308-0196.

December 30, 2002

*Ardin H. Marschel*  
ARDIN H. MARSCHEL  
PRIMARY EXAMINER